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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,610	12/10/1999	ELIZABETH G. NABEL	8642/88	9076

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/458,610	NABEL ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-112,114-119,121-135 and 138-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-112, 114-119,121-135 and 138-146* is/are rejected.

7)☒ Claim(s) *120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 8/22/05 has been entered. Claims 1-105, 113, and 136-137 are canceled. Claims 106-112, 114-135, and 138-146 are pending in the instant application. Applicant's declaration under 37 CFR 1.132 by Elizabeth Nabel, received on 8/22/05, has also been entered. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office actions.

All rejections over previously pending claims 113, and 136-137 have been withdrawn in view of the cancellation of these claims.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 7/26/05 was filed after the mailing date of the non-final rejection on 5/19/05. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed copy of the 1449 is attached to this action. However, please note that references A4-A8, while considered by the examiner, do not appear to be related to the subject matter of the instant application and claims as they are directed to antisense therapy.

Claim Rejections - 35 USC 112

The rejection of pending claims 109-112, 114-119, 121-135, and 138-142 under 35 U.S.C. 112, first paragraph, for lack of enablement is **maintained**. Applicant's amendments to the claims, arguments, and the declaration under 37 CFR 1.132 by Elizabeth Nabel, hereafter referred to as the second Nabel declaration, have been fully considered but have not been found persuasive in overcoming the following grounds of rejection of the claims for reasons of record discussed in detail below.

In view of the evidence provided by the second Nabel Declaration, the following scope of enablement has been identified: a method of treating a vascular injury in a mammal comprising delivery to a blood vessel at the site of injury transformed vascular smooth muscle cells or vascular endothelial cells, wherein the transformed vascular cells (i) originate from the mammal or are syngeneic to the mammal, (ii) comprise an exogenous nucleic acid encoding basic fibroblast growth factor, and (iii) express sufficient amounts of basic fibroblast growth factor in the mammal to treat said vascular injury.

Applicant's arguments and the evidence provided in the first and second Nabel declarations do not overcome the previously identified lack of enablement for the site specific installation of any transformed vascular cell or non-vascular endothelial, smooth muscle, or parenchymal cell, to any site including the bowel, liver, kidney, or heart, wherein the cells comprise any exogenous nucleic acid encoding a protein, or for the lack of enablement for treating atherosclerosis, thrombosis, rethrombosis, or other ischemic conditions in a mammal by

site specific installation of any transformed vascular cell or non-vascular endothelial, smooth muscle, or parenchymal cell, to any site including the bowel, liver, kidney, or heart, wherein the cells comprise any exogenous nucleic acid encoding a protein.

The applicant argues that the second Nabel declaration submitted with the instant response in combination with the first Nabel declaration and the teachings of the specification enable the breadth of the invention as claimed and that according to the MPEP , all that is required for enablement is a "reasonable correlation" between the scope of enablement and the scope of the claims, citing MPEP 2164.08 and *In re Fisher*. The applicant further reiterates their statement that the courts do not prohibit operativeness from being demonstrated by actual reduction to practice at any time. In response, MPEP section 2164.05(a) also clearly states that the specification must be enabling as of the filing date. In this case, the effective filing date is 1989. While the applicant is correct that post-filing evidence may be provided to demonstrate that the invention works, the MPEP clearly states, " However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention" (MPEP 2164.05). *Quigg v. Gould*, as previously cited by applicants, concurs with the MPEP, "post-filing evidence is relevant to enablement if it proves that the invention works as broadly as claimed". However, having carefully reviewed the evidence provided by both Nabel declarations it is found that the post-filing evidence of record, alone or in combination with the teachings of the

specification, does not enable the breadth of the claims as written. As discussed in detail in the previous office actions, the p27 gene utilized in the experiments disclosed in the first Nabel declaration was not known in the prior art as of 1989. The gene was not discovered until 1994. Thus, the material used in the experiments described in the declaration was not described in the specification or well known to one of skill in the art. Thus, it is clear that these experiments do not follow the guidance provided by the specification. Further, the declaratory evidence in the first Nabel declaration is not commensurate in scope with the claimed invention. As amended, the claims as written are broad and read generally on the expression of any recombinant protein by vascular cells implanted into a host mammal, and the treatment of various vascular conditions in a human patient by the installation of transformed endothelial, smooth muscle, or parenchymal cells. The single example provided in the first declaration demonstrates that the expression of p27 from vascular smooth muscle cells delivered by catheter to the femoral artery can inhibit catheter-induced neointimal hyperplasia. However, as noted above, the methods claimed read on the treatment of various types of vascular conditions including atherosclerosis, thrombosis, and restenosis in a patient by the instillation of any transformed vascular cell or transformed non-vascular endothelial, smooth muscle or parenchymal cell to any site. It is further noted that specific sites for installation of the cells recited in the claims include the heart, kidney, liver and bowel, which are not limited to the introduction of the cells into a blood vessel but include the introduction of the cells into cardiac muscle, renal glomeruli, intestinal epithelial and hepatic ductal epithelial tissue. The introduction of cells into a blood vessel is not commensurate in scope with the introduction of the cells into organ tissue based not only on the substantially different physiological environments of these tissues, but also on the fact that while the

expression of the protein by the transduced cells in the blood vessel allows direct contact of the protein or cells expressing the protein with the site of injury, the expression of the protein in other types of tissue requires the protein or cells to be transported from the site of delivery into the vessel and thus the site of injury. Further, the candidate proteins recited in the specification and now recited in claims 109 and 116 as putative therapeutic agents are all substantially different proteins with different biological properties and activities not related to p27. p27 is a cell cycle inhibitor that acts to inhibit cyclin-CDK complexes. Urokinase and tPA, now recited in the claims, are proteases which act to convert plasminogen to plasmin. TNF and TGF are both inflammatory cytokines. As such, even if p27 had been known in the art prior to the time of filing, a nexus between the activity of the cell cycle inhibitor p27 expressed from transformed vascular smooth muscle cells on neointimal hyperplasia and the activity of any other substantially different protein expressed by any vascular cell, or endothelium or parenchymal cells on injury induced neointimal hyperplasia or other types of ischemic diseases which differ substantially from injury induced neointimal hyperplasia cannot be made. As such, the declaratory data of the first Nabel declaration does not overcome the lack of enablement for the breadth of the methods as claimed because the evidence provided does not bear a reasonable correlation to scope of the claims as written.

The second Nabel declaration discloses the results of experiments wherein porcine vascular smooth muscle cells are transduced with an adenoviral vector encoding basic fibroblast growth factor (bFGF) and then introduced by catheter to the femoral artery at the site of catheter-induced vascular injury in pigs. The second declaration provides evidence that the expression of bFGF from the transduced vascular smooth muscle cells at the site of injury

reduced neointimal hyperplasia and arterial lesion formation compared to untreated controls. In view of the evidence presented in the second Nabel declaration, the instant action has identified the scope of enablement set forth above. However, the evidence provided is not found to be commensurate in scope with the claims as written. Like the first declaration, the experiments in the second declaration utilize vascular smooth muscle cells and are delivered directly to a blood vessel at the site of catheter induced vascular injury. In contrast, the claims as written read broadly on the use of any transduced vascular cell, or any transduced endothelial, smooth muscle, or parenchymal cell, and on the "site specific" installation of these cells to various sites including the bowel, heart, kidney or liver for the treatment of various conditions including thrombosis, atherosclerosis, and restenosis. Thus, both declarations solely disclose the use of vascular smooth muscle cells, and do not provide any evidence that other types of vascular cells or non-vascular endothelial, smooth muscle, or parenchymal cells could be used to successfully express therapeutic levels of bFGF or any other protein in an injury blood vessel such that injury induced hyperplasia is reduced or inhibited. The claims also read on the expression of any protein from the transduced cells, and specifically claim a number of proteins which include proteases such as urokinase and tPA, and inflammatory cytokines such as TNF and TGF. The growth factor bFGF does not share the same properties as the proteases and inflammatory cytokines listed above. Further, there is no evidence of record or in the prior art that any of the other proteins disclosed in the specification or recited in the claims other than bFGF have any therapeutic effect on injury induced neointimal hyperplasia or on any of the other conditions listed.

Further, in regards to the teachings of the specification as discussed in detail in the previous office actions, while the specification does in fact disclose a number of putative therapeutic proteins that could be used in applicant's methods, no data regarding the actual activity of these putative therapeutic proteins when expressed *in vivo* according to the instant methods has been presented in the specification. The specification's working examples demonstrate the transfection of vascular endothelial cells with a vector encoding lac-Z, and the installation of these cells by balloon catheter to blood vessels *in vivo*. The specification reports that the endothelial cells expressed detectable levels of beta-galactosidase following transplantation. The specification also states that expression could be detected for approximately six weeks. However, the specification does not correlate the level of beta-galactosidase with any therapeutic effect on any disease symptom or teach that the expression of similar levels of any other protein, such as FGF or tPA, for similar periods of time from transplanted endothelial cells or any other type of vascular cell would result in any effect on any cardiovascular condition such as atherosclerosis, restenosis, or heart disease, or any other type of ischemic in any organ including liver, kidney, or bowel.

Therefore, in summary, the factual evidence provided in both the Nabel declarations and in the working examples provided by the specification are limited to direct delivery of transduced vascular smooth muscle or vascular endothelial cells to a blood vessel. Further, regarding proteins to be expressed and in particular therapeutic proteins, the working examples utilize a non-therapeutic marker gene to demonstrate expression of protein from the transplanted transduced cells. The therapeutic effects of the p27 gene disclosed in the first Nabel declaration cannot be used as evidence of enablement as the p27 gene was not identified until years after the

effective filing date and thus was neither disclosed by the specification nor well known in the prior art. The second Nabel declaration does provide evidence that vascular smooth muscle cells transduced with a retrovirus encoding bFGF are capable of expressing sufficient amounts of bFGF at the site of balloon catheter induced vascular injury in a mammal to reduce neointimal hyperplasia. Therefore, as discussed in detail above, the evidence provided is not commensurate in scope with the claims as written. Based on the analysis of the evidence of record provided above, a "reasonable correlation" between the scope of enablement provided by the specification and the declaratory evidence and the scope of the claims does not exist.

Finally, the applicant argues that at least for claims 109-114, treating a disease or achieving a therapeutic effect is not limitation of the methods as claimed. The applicant argues that for claims 109-114, all that is required is the expression of the protein in the mammal. In response, claim 113 has been canceled. For claims 109-112 and 114, the claims, while reciting methods for introducing a protein in a mammal, the claims also recite specific proteins (claim 109), or identify the protein to be expressed as having specific functions such as the ability to induce angiogenesis (claim 110), the ability to induce revascularization (claim 111), the ability to be used in treatment of vascular injury, stenosis, restenosis, atherosclerosis, thrombosis, or rethrombosis (claim 112), and the ability to improve vascular or cerebrovascular circulation (claim 114). For claims 110-112, and 114, the functional language has patentable weight and thus has been analyzed based on the enablement provided by the specification for achieving these effects. Further, for all of claims 109-112 and 114, the specification clearly teaches that the purpose for expressing the specific proteins recited in these claims is for the treatment of various diseases. The specification does not identify any use for expressing any of the proteins of claims

109-112 and 114 that do not involve achieving some therapeutic effect on a vascular or ischemic condition in a mammal. Further, the previous office actions have demonstrated that at the time of filing, the skilled artisan did not consider the expression of therapeutic levels of protein for the treatment of disease as predictable. The references cited in the previous office action, Verma et al., Ledley et al., and Orkin et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. Thus, the skilled artisan would not have predicted at the time of the effective filing date of the instant application that the expression of any level of a putative therapeutic protein from transduced vascular or non-vascular endothelial, smooth muscle or parenchymal cells for any length of time in any type of tissue would result in a therapeutic effect on the disease to be treated.

Therefore, for reasons of record, as discussed in detail above, the rejection of record stands.

Double Patenting

The rejection of pending claims 106-109, 114-118, 121-131, and 142-146 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of U.S. Patent No. 6,203,991 (3/20/01), the '991 patent, is maintained. While the applicant again states that they disagree with the grounds of rejection, no specific arguments traversing the rejection have been presented. However, it is noted that the applicants state their

intention to file a terminal disclaimer upon the allowance of the rejected claims. As a terminal disclaimer has not yet been filed, the rejection of record stands.

Applicant is again advised that should claims 106-108 be found allowable, claims 143-146 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 120 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER